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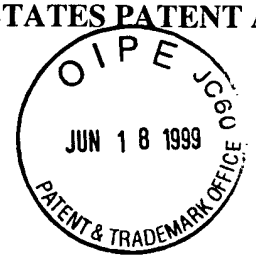
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Attorney Docket No. 077319/0129

In re patent application of
David PORUBEK, *et al.*
Serial No.: 08/932,834
Filed: September 18, 1997
For: COMPOUNDS HAVING SELECTIVE HYDROLYTIC POTENTIALS

Group Art Unit: 1611
Examiner: M. Berch

DECLARATION UNDER 37 CFR ∋ 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

I, Carolyn Paradise, hereby declare:

1. I am the Head of Medical Affairs for Cell Therapeutics, Inc., the assignee of the captioned application. I am a physician with over twenty years of experience in the field. My qualifications are set out in my *curriculum vitae*, which is attached hereto as APPENDIX A.

2. I have reviewed the subject application and the portions of the Office Actions pertaining to the therapeutic utility of lisofylline and the claimed compounds. As set out in detail below, it is my opinion that one skilled in the medical arts would recognize the therapeutic utility of the presently claimed compounds and could establish a suitable dosing regimen using methods routinely employed in standard clinical trials.

3. It is my understanding that the PTO is contending that the only reasonable utility for the presently claimed compounds is as a prodrug of lisofylline and lisofylline-like compounds. But, the Office further asserts that, since "no one has been able to figure out how to get lisofylline to actually work, ... getting these types of compounds to work requires undue experimentation." This statement is in error. In fact,

lisofylline is the subject FDA-sanctioned Phase II and Phase III clinical trials. Merely getting such trials approved require substantial indications of therapeutic efficacy. While lisofylline is not yet approved for clinical use, it is untrue to state that "no one has been able to figure out how to get lisofylline to actually work.

4. Moreover, the indications under clinical investigation are the very ones described in the present application. For example, in the specification at page 1, lisofylline is described as useful in several clinical applications, including, *inter alia*, "preventing multi-organ dysfunction associated with trauma." Indeed, based on these pharmacological activities of lisofylline, initial clinical trials were conducted, which bore out its therapeutic usefulness at this level. See attached literature at APPENDIX B

5. I have reviewed the lisofylline clinical literature from the perspective of a clinician, and I find no evidence that anything other than routine testing was used; the methodologies are standard. In other words, given the compound lisofylline and the therapeutic activity, evidenced in the specification, the clinician readily can determine a suitable treatment regimen, without employing anything other than routine experimentation. Moreover, I have every reason to believe that this is also true regarding the other compounds within the lisofylline family, like the presently claimed compounds.

6. In addition, I attach representative data from recent clinical studies that show lisofylline has a profound effect on the incidence of neutropenic infections in human bone marrow transplant patients. As seen by the figure at APPENDIX C, while 39% of patients receiving placebo suffered from an infection, none of the lisofylline-treated patients did. In addition, as seen by the figure at APPENDIX D, lisofylline also completely eliminated the incidence of fungal infections in particular, versus an incidence of 14% for controls. Consistent with the teaching of the specification, Abstract #2127, at APPENDIX E, also reports that lisofylline decreases the incidence of infection following traumatic injury to, for example the gut, that occurs during cytotoxic therapies.

7. As discussed in the foregoing paragraph, given the known therapeutic utility of the lisofylline class of compounds, a clinician could, via routine clinical procedures, select a suitable dosing scheme. In this regard, I also have reviewed the dosing information disclosed in the specification. As a clinician, I would use these numbers, at most, as a general benchmark. Rather, I would still proceed, using standard methods like those disclosed in the accompanying literature, to set a dosing protocol. Thus, to the extent that those numbers may be inconsistent with what would be used, for example, in standard dose-escalation protocols, the skilled clinician would recognize this.

8. I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: Carolyn Paradise
Carolyn Paradise, M.D.

Date: 6/17/98